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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Alisa Harbin, Esq. Novartis Vaccines and Diagnostics, Inc. Intellectual Property - R440 P. O. Box 8097 Emeryville, CA 94662				
EXAMINER				
FUBARA, BLESSING M				
ART UNIT		PAPER NUMBER		
1618				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/775,964

Applicant(s)

FANG ET AL.

Examiner

BLESSING M. FUBARA

Art Unit

1618

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 30 July 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 34-42 and 62-76 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 34-42 and 62-76 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/06)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

The examiner acknowledges receipt of request for extension of time, amendment and remarks, all filed 7/30/08. No claim is amended. Claims 34-42 and 62-76 are pending.

Response to Arguments

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

2. Claims 34-42 and 62-76 remain rejected under 35 U.S.C. 102(a) as being anticipated by O'Hagan et al. (WO 00/50006) for reasons of record and reiterated herein below.

O'Hagan discloses method of preparing microparticles by forming microemulsion by combining an organic solvent and polymer that is selected from the group consisting of poly(α -hydroxy acid), a polyhydroxy butyric acid, polycaprolactone, polyorthoester, polyanhydride and polycyanoacrylate and anionic or cationic detergent, removing the organic solvent and recovering the microparticles (page 7, last full paragraph, pages 8-11) by filtration (Example 2). The % amount of detergent that in the microparticles in claims 34, 37, 39 and 62-68. Macromolecules such as polynucleotides and polypeptides are adsorbed onto the particles (page 2, 4th full paragraph) meeting claims 34, 37, 39 and 72-76. The CTAB used (Tables 19A and 19B) meets claims 38 and 40.

Response to Arguments

3. Applicant's arguments filed 7/30/08 have been fully considered but they are not persuasive.
4. Applicant argues that the microparticles of the invention are filtered and are not subjected to washing step, such that the ratio 10-90% of the total detergent in the microparticle is bound to the microparticle and the remainder is unbound while O'Hagan describes washing and centrifugation according to Examples 1-3 of O'Hagan; these arguments are directed as applicant iterates that O'Hagan does not teach limitation II, which requires the absence of washing step and limitation I, which requires a filtration step. The examiner disagrees because the claims are directed to limitation I, filtration or limitation II, absence of a wash step; the filtration limitation does not exclude a wash step since the comprising language of the method is open and second part of claim 34, Limitation II, in which the microparticles are not subjected to a washing step is an alternate embodiment because it is one or the other (see claim 34(b)). O'Hagan meets the requirements of the limitation in the first aspect that is limitation I, filtration. The limitation that the detergent is about 10-90 is inherent when the microparticles are formed according to 34 (a).

Claim Rejections - 35 USC § 103

5. Claims 34-42 and 62-76 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (US 6,395,253) in view of Paliard et al. (US 6,562,346) for reasons of record and reiterated herein below.

LEVY discloses preparation of microspheres that contain DNA or RNA as the bioactive agent (column 4, lines 31, 54 and 55). LEVY prepares a double emulsion of water-in-oil-in-

water emulsion by using a condensing agent in one phase and the method comprises the steps of: “(a) dissolving at least one polymer in a water-immiscible organic solvent to yield an organic phase; (b) dissolving a polyanionic bioactive agent in aqueous solution to yield a first aqueous phase; (c) emulsifying the organic and first aqueous phases to yield a first milky emulsion; (d) dissolving a condensing agent in aqueous solution to yield a second aqueous phase; (e) emulsifying the first milky emulsion and the second aqueous phase to yield a second milky emulsion; and (f) removing the organic solvent from the second milky emulsion to yield microspheres containing condensed polyanionic bioactive agent with the emulsion meeting claims 34, 35 and 36-39. “The removal of the organic solvent in the final step is preferably by means of evaporation,” in one illustrative embodiment (column 4, lines 44 and 45). DNA and RNA are macromolecules and are polynucleotides meeting the requirements of claims 74-76. The concept of microspheres meets the microparticle limitation of claims 34, 37, 39, 42, 62, 65-70. Regarding the recitation that the microparticles are not subjected to washing step, it is noted that while the examples in Levy disclose a wash step, the basic preparation disclosed by Levy in section 4.2 does not state a wash step but rather that the microspheres are collected by ultracentrifugation and the alternative protocol disclosed in 4.6 and the comprising language is open. Levy uses 0.1% detergent (SDS in this case). There is no demonstration in applicants’ specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. The claims do not recite amount of detergent added to make the microparticle in the emulsion.

Regarding claim 36, which is directed to the process of cross-flow filtration, it is noted that in the cross-flow filtration process of the examined application, four liters of deionized water

(Example 5) is used to remove the detergents and this appears to be equivalent to washing so that the cross-filtration step of the claim 34 reads on optional wash step of one of embodiments of Levy at column 13, line 5; at column 18, line 42 (washed with tris-EDTA); at column 20, line 2 (cells washed with PBS buffer). There is also no demonstration that the cross-filtration step performed after removing the organic solvent provides unusual results; Levy discloses filtration as one of the steps. The filtration step in Levy meets the filtration step in claims 34 and 37.

Regarding the ratio of lactide to glycolide, it is noted that there is no demonstration by applicants that the recited ratio provides unusual/expected results. The silence of Levy on the ratio of lactide to glycolide is an indication that the lactide/glycolide can be used in any desired ratio that would be effective as a condensing agent for the DNA or RNA macromolecules. Levy also teaches polypeptide (column 4, line 64) meeting claim 72 and the SDS meets claim 71.

Regarding new claims 68-70, Levy in one of the embodiments does not wash the product but removes the solvent from the emulsion by evaporation so that the detergent is not removed or washed off (column 12, lines 58-67).

Levy uses SDS detergent. While Levy does not specifically state the presence of bound detergent in the amounts recited in the claims, it is noted that Levy does not specifically state that the microspheres/particles formed are free of detergent; and it flows from one of the embodiment that does not use a wash step but evaporates off the organic solvent (column 12, lines 58-67) that the detergent is not removed and as such, the microparticles would have detergent associated. However, while Levy teaches SDS and TWEEN, Levy does not disclose the use of cetyl trimethyl ammonium bromide (CTAB) detergent. But Paliard discloses an emulsion that comprises PLG polymer and CTAB (Example 5). Thus Paliard is relied upon for a teaching that

the specific CTAB detergent can be used with PLG in an emulsion. CTAB and the SDS meet the detergent limitations of claims 38, 40, 68, 71. Therefore, taking the teachings of the references together, one having ordinary skill in the art at the time at the invention was made would have reasonable expectation of success that including the detergent CTAB in the double emulsion of Levy would produce emulsion whose particles would effectively adsorb polynucleotides and polypeptides that would be expected to release/deliver the polynucleotide and the polypeptide as desired.

Response to Arguments

6. Applicant's arguments filed 7/30/08 have been fully considered but they are not persuasive.

Applicant argues that a) Levy and Paliard do not meet the threshold of prima facie case of obviousness because Levy does not teach or suggest adsorption to microparticles but "rather describes methods of incorporating nucleic acids into polymeric microspheres and/or nanospheres (micro-encapsulation) through the use of condensing agent," according to the abstract and title of Levy; that the biologically active macromolecule is added in step (c) such that it is adsorbed to the surface of the microparticles so that applicant contends that the teachings of Levy are not relevant to the pending claims.

The examiner disagrees with regards to (a) above. Applicant appears to be arguing that because the order of performing the steps in the process of making the microparticle composition is not the same order as those in the claims, Levy is not applicable. However, it is brought to applicant's attention that the rejection is not one of anticipation but one in which the claimed process is rendered obvious by the method of Levy; secondly, selection of any order of

performing process steps is prima facie obvious in the absence of new or unexpected results. Applicant has not provided factual evidence that the exact order of performing the method steps provides unexpected results over the method of the prior art.

b) Levy neither teaches nor suggests microparticle composition in which about 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder is unbound. The examiner disagrees with regards to (b) because the binding of the detergent happens when the emulsion is formed and because emulsion is formed in Levy, the detergent is inherently adsorbed onto the particles noting that the claims do not recite any specific amounts of detergent use in the preparation of the microparticle composition.

c) That the solvent evaporation step referred to by the examiner is not an alternative to washing but rather is a process that is used to yield solid microparticles from dispersed oil phase. With regards to (c), the examiner does not agree with applicant that the examiner has equated solvent evaporation with a wash step. Rather, the office action of 04/04/08, at page 5, first full paragraph, says that the solvent from the emulsion is removed by evaporation.

d) That "absent a reason to ensure that unbound detergent remains in the microparticles, one of ordinary skill would be motivated to wash the microparticles of excess detergent by centrifugation as taught by Levy," and as indicated in Singh et al. in the Proc. Natl. Acad. Sci. USA, 2000, 97:811-816. As it regards to (d), the examiner disagrees with applicant's reasoning for motivation to wash the microparticle as per Singh because the Singh reference has not been used in the rejection. Furthermore applicant's demands that "absent a reason to ensure that unbound detergent remains in the microparticles, one of ordinary art would be motivated to wash the microparticles of excess detergent by centrifugation," is not persuasive because "When the

PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). In the present case, applicant has not provided factual showing to support applicant’s position and the PTO cannot provide factual reasoning because, the PTO does not have laboratory facility to provide the factual evidence as required by the applicant while at the same time the applicant has notably not provided factual evidence that the particles of Levy contains less than the amount of the detergent claimed. It is also noted Levy does not say to wash the particles to remove excess detergent.

e) That in order for inherency to operate in Levy, the claimed amount of unbound and bound detergent must be provided in Levy.

The examiner disagrees with regards to (e) above because the claims did not state the amount of detergent in the composition that would provide the claimed amount of bound detergent in the broad range claimed. It is the combination of detergent, water, polymer and organic solvent to form emulsion and the subsequent removal of the organic solvent from the emulsion that leads to the microparticles that has the 10-90% detergent bound to the microparticle. By the same token, the combination of detergent, water, polymer and organic solvent to form emulsion with subsequent removal of the organic solvent from the emulsion would lead to the microparticles that would inherently have the 10-90% detergent bound to the microparticle.

f) That the absence of a wash step would not necessarily produce the amount of bound or unbound detergent. The examiner does not agree because the claims dictate that the broad range in the amount of bound detergent is not derived from any specific initial amount of detergent in

composition, but the silence in the amount of the initial amount of detergent suggests that any amount of detergent would lead to an amount of detergent bound to the microparticles.

Applicant's arguments as they regard to (f) are thus not persuasive.

g) That Levy does not teach the claimed method since the SDS is added after the formation of DNA containing microspheres, but, secondly, selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results.

h) That Paliard does not make up for the deficiencies in Levy because considering the totality of the reference, it would not have been obvious to use CTAB in place of SDS since SDS was used an analytical reagent in Levy in unbound form and from the teachings of Singh, it is a strong incentive to keep the detergent levels to a minimum. But, keeping the levels of detergent to a minimum is relative and a range of 10-90% Furthermore, the 10-90% detergent is based on the total amount of the detergent in the composition and the total amount of the detergent was never claimed. The examiner also disagrees with the applicant that Levy only uses SDS as an analytical reagent because column 12, lines 47-54 of Levy teaches the use of emulsifying agents such as SDS, TWEEN, etc in an emulsion that contains PLG. Thus, Levy does not just use SDS as an analytical reagent. Paliard was relied upon for teaching that specific CTAB detergent can be used with PLG containing emulsion so that the use of one detergent in place of another would lead to the expected formation of an emulsion.

Applicant in arguments a) through h) is arguing against the individual references when a combination of references is used in the rejection. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references.

See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

7. Claims 34, 35, 36 and 42 remain rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hagan et al. (US 6,086,901) for reasons of record and reiterated herein below.

O'Hagan discloses the process of preparing an emulsion that comprises poly(lactide-glycolide), solvent and detergent (Example 1); O'Hagan discloses that the size of the droplets (particle, microsphere) depends on the ratio of the detergent to oil (column 12, lines 38-47) and also that water-in-oil-water (w/o/w) type emulsion can be formed of the microparticle (column 10, lines 9-20). The process of claim 36 reads on washing because in the cross-flow filtration process, 4 liters of deionized water (Example 5) are used and the removal of the water appears to approximate the process of filtration/washing. Emulsion and particles meet the emulsion and particle requirements of claims 34, 35 and 43. Claim 42 is a product by process claim and O'Hagan's particles meet the claim. While O'Hagan discloses a washing step, there is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. Therefore, taking the teaching of the prior art, one having ordinary skill in the art at the time the invention was made would have reasonable expectation of success to prepare biodegradable microparticles for administration to vertebrates to effect immunization.

Response to Arguments

8. Applicant's arguments filed 1/14/08 have been fully considered but they are not persuasive.

Applicant argues that O'Hagan teaches a wash step and cannot therefore render obvious the claimed method, but, the claims recite broad category of filtration which applicant argues results in unbound and bound detergent. Also, claim 34(b) requires a filtration step or method that does not require a washing step. The filtration step does not exclude a wash step in view of the open comprising language. The generic filtration process provides bound or unbound detergent, it flows that the O'Hagan's filtration of composition containing particles and detergent would also provide unbound and bound detergent. Furthermore, the comprising language of the claims is open permitting the presence of other steps and selection of any order of performing process steps is prima facie obvious in the absence of new or unexpected results.

No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Michael G. Hartley/
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/Blessing M. Fubara/
Examiner, Art Unit 1618